



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 9/12, 9/127	A1	(11) International Publication Number: WO 00/37053 (43) International Publication Date: 29 June 2000 (29.06.00)
(21) International Application Number: PCT/CA99/01233 (22) International Filing Date: 16 December 1999 (16.12.99) (30) Priority Data: 60/113,242 21 December 1998 (21.12.98) US 09/397,701 16 September 1999 (16.09.99) US (71) Applicant (for all designated States except US): GENEREX PHARMACEUTICALS INC. [CA/CA]; 202, 33 Harbour Square, Toronto, Ontario M5J 2G2 (CA). (72) Inventor; and (75) Inventor/Applicant (for US only): MODI, Pankaj [CA/CA]; 519 Golf Links Road, Ancaster, Ontario L9G 4X6 (CA). (74) Agents: KAO, Dolly et al.; Barrigar & Moss, Suite 901, 2 Robert Speck Parkway, Mississauga, Ontario L4Z 1H8 (CA).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: LARGE MOLECULE DRUG DELIVERY SYSTEM USING AEROSOLIZED MEMBRANE-MIMETIC AMPHIPHILES		
(57) Abstract <p>A mixed liposome pharmaceutical formulation with multilamellar vesicles, comprises a proteinic pharmaceutical agent, water, an alkali metal lauryl sulphate in a concentration of from 1 to 10 wt./wt.%, at least one membrane-mimetic amphiphile and at least one phospholipid. The amount of each membrane mimetic amphiphile and phospholipid is present in a concentration of from 1 to 10 wt./wt.% of the total formulation, and the total concentration of membrane mimetic amphiphiles and phospholipids is less than 50 wt./wt.% of the formulation. The formulation may be administered to the buccal cavity using a metered dose dispenser.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

LARGE MOLECULE DRUG DELIVERY SYSTEM USING AEROSOLIZED MEMBRANE-MIMETIC AMPHIPHILES

This is a continuation of Application No. 60/113242
5 filed December 21, 1998.

Field of the Invention

The present invention relates to an improved
delivery system for the administration of large-molecule
pharmaceuticals, e.g. peptidic drugs, vaccines and
10 hormones. In particular it relates to pharmaceuticals
which may be administered through the oral and nasal
membranes, or by pulmonary access.

Background to the Invention

New methods of delivering large macromolecules
15 (proteins and peptides) continue to be sought. One of
the avenues investigated concerns the use of membrane-
mimetic amphiphiles. A study of membrane-mimetic
amphiphiles extends back to the first decade of the 20th
century. Experiments using physical and chemical
20 methods have shown that such molecules assume preferred
arrays in the presence of water. Formation of these
arrays, which includes micelles, monolayers and
bimolecular layers is driven by the need of the polar
head groups, which may be ionogenic or not, to associate
25 with water, and the need of the polar hydrophobic tails
to be excluded from water, (Small, D; Handbook of Lipid
Research, vol. 4, 1986; Tanford, J: The Hydrophobic
Effect, John Wiley & Sons, 1980; Fendler, J. Membrane
Chemistry, 1982). Exactly which type of structure is
30 assumed depends on upon the nature of the amphiphile,
its concentration, the presence of other amphiphiles,
temperature and the presence of salts and other solutes
in the aqueous phase.

Membrane-mimetic amphiphiles include molecules that
35 are insoluble in water but can take up water, and
molecules that have appreciable solubility in water

- 2 -

under limiting conditions. The former amphiphiles do not form molecularly disperse solutions in water but may swell considerably with water to form lamellar phases. The latter amphiphiles can, at some temperatures, form solutions of dispersed monomers in water and often undergo the following sequence as the concentration in water is increased: monomeric solution to micellar solution. The manufacture of non-phospholipid liposomes, depends on the manipulation of environmental variables (e.g. temperature, hydration and composition) in an appropriate temporal sequence so as to cause non-phospholipid amphiphiles to form liposomal structures.

Gebicki et al. (Nature, 243, 232, 1973; Chem. Phys. Lipids, 16, 142, 1976; Biochem. Biophys. Res. Commun. 80, 704, 1978; Biochemistry, 17, 3759, 1978) demonstrated the formation of water containing vesicles enclosed by oleic acid. Others, as disclosed for example in U.S. Patents 4 772 471 and 4 830 857, and in J. Microencapsul. 4, 321, 1987, have made lipid vesicles from single tailed ether or esters derivatives of polyglycerol. These liposomes were found suitable for cosmetic products. Murakami et al (J. Am. Chem. Soc, 101, 4030, 1979; J. Am Oil Chem Soc. 66, 599, 1989) formed single compartment vesicles with one or more bilayer walls composed of cationic amphiphiles involving amino acid residues. Kaler et al (Science, 245, 1371, 1989) demonstrated that appropriate aqueous mixtures of single-tailed cationic and anionic surfactants spontaneously form single-walled vesicles, presumably via salt formation. Others have developed methods for manufacture of paucilamellar, non-phospholipid liposomes that can be formed from a variety of amphiphiles as well as from certain phospholipids. The liposomes have two or more membranes surrounding an amorphous core, each membrane being composed of amphiphile molecules in

- 3 -

bilayer array. The core accounts for most of the vesicle volume and encapsulating substances.

The above-mentioned non-phospholipid based liposomes are mainly used for the delivery of
5 moisturizers and cosmetic ingredients used topically or externally as creams or moisturizers. In some cases such liposomes may be used as an ointment for delivery of some pharmaceutical products. Many ingredients utilized in the above products have been found to be
10 inadmissible in the human body and are not approved by the regulatory agencies around the world for the purpose of oral administration and as a vehicle for delivery of macromolecules (proteins and peptides) as life saving therapeutics. Furthermore, other non-phospholipid based
15 liposomes have been developed for non-pharmaceutical applications, e.g. water-borne oil paints, surface cleansers, heavy duty industrial cleansers and skin-cleansing detergents.

Certain aspects of the present invention aims at
20 the development of oral compositions consisting of mixture of certain non-phospholipid based membrane-mimetic amphiphiles (suitable and approved by the regulating agencies for oral formulation of human pharmaceutical products) in combination of specific
25 phospholipids to form multilamellar liposomes which are very stable and are smaller than the pores of the gastrointestinal (GI) tract.

Relatively very little progress has been made in reaching the target of safe and effective oral
30 formulations for peptides and proteins. The major barriers to developing oral formulations for proteins and peptides include poor intrinsic permeability, luminal and cellular enzymatic degradation, rapid clearance, and chemical stability in the GI tract.
35 Pharmaceutical approaches to address these barriers,

- 4 -

which have been successful with traditional small, organic drug molecules, have not readily translated into effective peptide and protein formulations. Although the challenges are significant, the potential therapeutic benefits remain high especially in the field of diabetes treatment using insulin.

Researchers have explored various administration routes other than injection for proteins and peptides. These routes include administration through oral, intranasal, rectal, vaginal cavities for the effective delivery of large molecules. Out of the above four mentioned routes oral and nasal cavities have been of greatest interest. Both the oral and nasal membranes offer advantages over other routes of administration. For example, drugs administered through these membranes have a rapid onset of action, provide therapeutic plasma levels, avoid a first pass effect of hepatic metabolism, and avoid exposure of the drug to a hostile GI environment. Additional advantages include easy access to the membrane sites so that the drug can be applied, localized and removed easily. Further, there is a good potential for prolonged delivery of large molecules through these membranes.

The oral routes have received far more attention than have the other routes. The sublingual mucosa includes the membrane of ventral surface of the tongue and the floor of the mouth whereas the buccal mucosa constitutes the lining of the cheek. The sublingual mucosa is relatively permeable thus giving rapid absorption and acceptable bioavailability of many drugs. Further, the sublingual mucosa is convenient, acceptable and easily accessible. This route has been investigated clinically for the delivery of a substantial number of drugs.

Various mechanisms of action of penetration of

- 5 -

large molecules using enhancers have been proposed. These mechanisms of action, at least for protein and peptidic drugs include (1) reducing viscosity and/or elasticity of mucous layer, (2) facilitating
5 transcellular transport by increasing the fluidity of the lipid bilayer of membranes, (3) facilitating paracellular transport by altering tight junction across the epithelial cell layer, (4) overcoming enzymatic barriers, and (5) increasing the thermodynamic activity
10 of drugs (Critical Rev. 117-125, 1992).

Many penetration enhancers have been tested so far and some have been found effective in facilitating mucosal administration of large molecular drugs. However, hardly any penetration enhancing products have
15 reached the market place. Reasons for this include lack of a satisfactory safety profile respecting irritation, lowering of the barrier function, and impairment of the mucocilliary clearance protective mechanism. It has been found that some of the popular penetration
20 enhancers, especially those related to bile salts, and some protein solubilizing agents, impart an extremely bitter and unpleasant taste. This makes their use impossible for human consumption on a day to day basis. Several approaches were utilized to improve the taste of
25 the bile salts based delivery systems, but none of them are commercially acceptable for human consumption to date. Approaches utilized include patches for buccal mucosa, bilayer tablets, controlled release tablets, liposome formulations, use of protease inhibitors,
30 buccally administered film patch devices, and various polymer matrices. Further the problem is compounded because of the localized side effect of a patch which often results in severe tissue damage in the mouth.

The absorption of proteins and peptides is believed
35 to be enhanced by the diffusion of large molecules

- 6 -

entrapped in the mixed micellar form through the aqueous pores and the cell structure perturbation of the tight paracellular junctions.

It has now been found that improvements in
5 penetration and absorption of certain mixed micellar formulations can be achieved by mixing the mixed micellar formulation with propellants such as tetrafluoroethane, heptafluoroethane, dimethylfluoropropane, tetrafluoropropane, butane,
10 isobutane, dimethyl ether and other non-CFC and CFC propellants, especially when delivered (e.g. applied to the buccal mucosa) through aerosol devices, e.g. metered dose inhalers (MDIs). Metered dose inhalers are a proven technology and a popular drug delivery form for
15 many kinds of drug. The use of the present novel formulations and excipients can improve the quality (in terms of absorption), stability and performance of MDI formulations. The formulation ingredients are selected specifically to give enhancement in the penetration
20 through the pores and facilitate the absorption of the drugs to reach therapeutic levels in the plasma. With the proper formulation changes and changes in administration technique, the formulation can be delivered to the deep lungs, through the nasal cavity
25 and the buccal cavity.

Pressurized inhalers also offer a wide dosing range, consistent dosing efficiency. In this local delivery greater than 95% of the dose is reached to the target area. The smaller particle size (4-15 microns)
30 of pressurized inhalers also enhances dosing due to broader coverage within the buccal cavity. In this situation, increased coverage can help more absorption of drug like insulin. Furthermore, because these devices are self-contained, the potential for contamination is
35 avoided.

- 7 -

Summary of the Invention

Accordingly the present invention provides an aerosol pharmaceutical formulation with multilamellar vesicles, comprising i) a pharmaceutical agent, ii) water, iii) an alkali metal C8 to C22 alkyl sulphate in a concentration of from 1 to 10 wt./wt.% of the total formulation, iv) at least one membrane-mimetic amphiphile, v) at least one phospholipid, vi) a phenol selected from the group consisting of phenol and methyl phenol in a concentration of from 1 to 10 wt./wt.% of the total formulation, and vi) a propellant selected from the group consisting of C1 to C2 dialkyl ether, butanes, fluorocarbon propellant, hydrogen-containing fluorocarbon propellant, chlorofluorocarbon propellant, hydrogen-containing chlorofluorocarbon propellant, and mixtures thereof,

wherein the membrane-mimetic amphiphile is selected from the group consisting of lauramidopropyl betain, lauramide monoisopropanolamide, sodium cocoamphopropionate, bishydroxypropyl dihydroxypropyl stearammonium chloride, polyoxyethylene dihydroxypropyl stearammonium chloride, dioctadecyldimethylammonium chloride, sulphasuccinates, stearamide DEA, sodium tauro dihydro fusidate, fusidic acid, alkali metal isostearyl lactylates, alkaline earth metal isostearyl lactylates, panthenyl triacetate, cocamidopropyl phosphatidyl PG-diammonium chloride, stearamidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidylcholine, polysiloxy pyrrolidone linoleyl phospholipid, octylphenoxypolythoxyethanol, and combinations thereof, and

wherein the phospholipid is selected from the group consisting of, phospholipid GLA (glycolic, lactic acid), phosphatidyl serine, phosphatidylethanolamine,

- 8 -

inositolphosphatides, dioleoylphosphatidylethanolamine, polysiloxy pyrrolidone linoleyl phospholipid, sphingomyelin, ceramides, cephalin, triolein, unsaturated lecithin, saturated lecithin and
5 lysolecithin, and combinations thereof, and

wherein the amount of each membrane-mimetic amphiphile and phospholipid is present in a concentration of from 1 to 10 wt./wt.% of the total formulation, and the total concentration of membrane-
10 mimetic amphiphiles and phospholipids is less than 50 wt./wt.% of the formulation.

Preferably the mixed liposome pharmaceutical formulation has a pH of between 6.0 and 8.0.

The preferred number of membrane mimetic
15 amphiphiles are from 2 to 5.

The preferred number of phospholipids are from 1 to
4.

In one embodiment, the alkali metal C8 to C22 alkyl sulphate is sodium C8 to C22 alkyl sulphate, and
20 preferably is sodium lauryl sulphate.

Preferably, the ratio of proteinic pharmaceutical agent, e.g. insulin, to propellant is from 5:95 to 25:75.

In a further embodiment, the methyl phenol is
25 m-cresol.

In another embodiment, the propellant is selected from the group consisting of tetrafluoroethane, tetrafluoropropane, dimethylfluoropropane, heptafluoropropane, dimethyl ether, n-butane and
30 isobutane.

In yet another embodiment, the mixed micellar pharmaceutical formulation is contained in an aerosol dispenser.

In a preferred embodiment at least one protease
35 inhibitor is added to the formulation to inhibit

- 9 -

degradation of the pharmaceutical agent by the action of proteolytic enzymes. Of the known protease inhibitors, most are effective at concentrations of from 1 to 3 wt./wt.% of the formulation.

5 Non-limiting examples of effective protease inhibitors are bacitracin, soyabean trypsin, aprotinin and bacitracin derivatives, e.g. bacitracin methylene disalicylate. Bacitracin is the most effective of those named when used in concentrations of from 1.5 to
10 2 wt./wt.%. Soyabean trypsin and aprotinin may be used in concentrations of about 1 to 2 wt./wt.% of the formulation.

Preferably the lecithin is saturated lecithin.

It will be recognized by those skilled in the art
15 that for many pharmaceutical compositions it is usual to add at least one antioxidant to prevent degradation and oxidation of the pharmaceutically active ingredients. It will also be understood by those skilled in the art that colorants, flavouring agents and non-therapeutic
20 amounts of other compounds may be included in the formulation.

In one embodiment the antioxidant is selected from the group consisting of tocopherol, deteroxime mesylate, methyl paraben, ethyl paraben and ascorbic acid and
25 mixtures thereof. A preferred antioxidant is tocopherol.

The pharmaceutical agent may be selected from a wide variety of macromolecular agents, depending on the disorder being treated, generally with molecular weights
30 greater than about 1000 and especially between about 1000 and 2 000 000. Pharmaceutical agents useful in the present invention include insulin, heparin, low molecular weight heparin, hirugen, hirulos, hirudin, interferons, interleukins, cytokines, mono and
35 polyclonal antibodies, chemotherapeutic agents,

- 10 -

vaccines, glycoproteins, bacterial toxoids, growth hormones, parathyroid hormone (PTH), leutenizing hormones, oestrogens, androgens, calcitonins, insulin like growth factors (IGF), glucagon like peptides (GLP-1 and GLP-2), steroids and retinoids, injectable large molecule antibiotics, protein based thrombolytic compounds, platelet inhibitors, DNA, gene therapeutics, RNA and antisense oligonucleotides and small molecule drugs.

10 The present invention also provides a metered dose aerosol dispenser with the aerosol pharmaceutical formulation of the present invention therein.

 The present invention also provides a method for administering an aerosol pharmaceutical formulations of the present invention, by spraying a predetermined amount of the formulation into the mouth with a metered dose spray device.

 The present invention also provides a method for administration of a proteinic pharmaceutical agent in a buccal cavity of a human being by spraying into the cavity, without inhalation, from a metered dose spray dispenser, a predetermined amount of an aerosol pharmaceutical formulation with multilamellar vesicles, comprising i) a pharmaceutical agent, ii) water, iii) an alkali metal C8 to C22 alkyl sulphate in a concentration of from 1 to 10 wt./wt.% of the total formulation, iv) at least one membrane-mimetic amphiphile, v) at least one phospholipid, vi) a phenol selected from the group consisting of phenol and methyl phenol in a concentration of from 1 to 10 wt./wt.% of the total formulation, and vi) a propellant selected from the group consisting of C1 to C2 dialkyl ether, butanes, fluorocarbon propellant, hydrogen-containing fluorocarbon propellant, chlorofluorocarbon propellant,

20
25
30

- 11 -

hydrogen-containing chlorofluorocarbon propellant, and mixtures thereof,

wherein the membrane-mimetic amphiphile is selected from the group consisting of lauramidopropyl betain, 5 lauramide monoisopropanolamide, sodium cocoamphopropionate, bishydroxypropyl dihydroxypropyl stearammonium chloride, polyoxyethylene dihydroxypropyl stearammonium chloride, dioctadecyldimethylammonium chloride, sulphosuccinates, stearamide DEA, sodium tauro 10 dihydro fusidate, fusidic acid, alkali metal isostearyl lactylates, alkaline earth metal isostearyl lactylates, panthenyl triacetate, cocamidopropyl phosphatidyl PG-diammonium chloride, stearamidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidyl PG- 15 diammonium chloride, borage amidopropyl phosphatidylcholine, polysiloxo pyrrolidone linoleyl phospholipid, octylphenoxypolythoxyethanol, and combinations thereof, and

wherein the phospholipid is selected from the group 20 consisting of, phospholipid GLA (glycolic, lactic acid), phosphatidyl serine, phosphatidylethanolamine, inositolphosphatides, dioleoylphosphatidylethanolamine, polysiloxo pyrrolidone linoleyl phospholipid, sphingomyelin, ceramides, cephalin, triolein, 25 unsaturated lecithin, saturated lecithin and lysolecithin, and combinations thereof, and

wherein the amount of each membrane-mimetic amphiphile and phospholipid is present in a concentration of from 1 to 10 wt./wt.% of the total 30 formulation, and the total concentration of membrane-mimetic amphiphiles and phospholipids is less than 50 wt./wt.% of the formulation.

Detailed Description of Preferred Embodiments

When developing new pharmaceutical formulations, it 35 is desirable to provide dosage forms suitable for

- 12 -

administering proteinic and peptidic drugs to humans and animals through oral, nasal, pulmonary and transdermal mucosal routes and to allow easy accessibility to the sites of administration. Local absorption of
5 macromolecular drugs is desirable over a prolonged period to maximize drug absorption. Furthermore, it is desirable to minimize tissue damage and provide acceptable tissue compatibility of the dosage form. It is preferable to provide systems which are pain free and
10 easy to be administered with great flexibility, in order to gain high acceptance and compliance of any therapy by patients.

It has been found that macromolecular drugs may be administered in liposomal formulations in which particle
15 sizes (1 to 4 nm) are smaller than any pores of mucosal surfaces.

The present invention provides an improved method for delivery of macromolecular (high molecular weight) pharmaceutical agents, particularly through the skin or
20 membranes in the nose, mouth or lungs. The preferred delivery is through oral or nasal cavities or through the lungs. The pharmaceutical agents cover a wide spectrum of agents, including proteins, peptides, hormones, vaccines and drugs. The molecular weights of
25 the macromolecular pharmaceutical agents are preferably above 1000, especially between 1000 and 2 000 000.

For example, hormones which may be administered with the present invention include human growth hormones, parathyroid hormones, follicular stimulating
30 hormones, luteinizing hormones, androgens, oestrogens, prostoglandins, somatotropins, gonadotropins, erythropoetin, interferons, interleukins, steroids and cytokines.

Vaccines which may be administered with the present
35 invention include bacterial and viral vaccines such as

- 13 -

vaccines for hepatitis A, hepatitis B, hepatitis C, influenza, tuberculosis, canary pox, chicken pox, measles, mumps, rubella, pneumonia, BCG, HIV, helicobacter pylori and AIDS.

5 Bacterial toxoids which may be administered using the present invention include diphtheria, tetanus, pseudomonas A and mycobacterium tuberculosis.

Examples of specific cardiovascular or thrombolytic agents include heparin, low molecular
10 weight heparin, hirugen, hirulos and hirudin.

Small molecules may also be administered using the present invention. For example, opioids, narcotics, analgesics, NSAIDS, steroids, anaesthetics, hypnotics and pain killers, may be administered with the aerosol
15 formulation of the present invention.

For insulin-containing and some other compositions, the composition may also contains at least one inorganic salt which opens channels in the gastrointestinal tract and may provide additional stimulation to release
20 insulin. Non-limiting examples of inorganic salts are sodium, potassium, calcium and zinc salts, especially sodium chloride, potassium chloride, calcium chloride, zinc chloride and sodium bicarbonate.

It will be recognized by those skilled in the art
25 that for many pharmaceutical compositions it is usual to add at least one antioxidant to prevent degradation and oxidation of the pharmaceutically active ingredients. It will also be understood by those skilled in the art that colorants, flavouring agents and non-therapeutic
30 amounts of other compounds may be included in the formulation. Typically flavouring agents are menthol and other fruit flavours.

The antioxidant is selected from the group

- 14 -

consisting of tocopherol, deteroxime mesylate, methyl paraben, ethyl paraben and ascorbic acid and mixtures thereof. A preferred antioxidant is tocopherol.

In a preferred embodiment at least one protease
5 inhibitor is added to the formulation to inhibit degradation of the pharmaceutical agent by the action of proteolytic enzymes. Of the known protease inhibitors, most are effective at concentrations of from 1 to 3 wt./wt.% of the formulation.

10 Non-limiting examples of effective protease inhibitors are bacitracin, soyabean trypsin, aprotinin and bacitracin derivatives, e.g. bacitracin methylene disalicylate. Bacitracin is the most effective of those named when used in concentrations of from 1.5 to 2
15 wt./wt.%. Soyabean trypsin and aprotinin two may be used in concentrations of about 1 to 2 wt./wt.% of the formulation.

It is believed that the phenolic compounds act mainly as preservatives and complexing agents to
20 stabilize drugs, e.g. insulin. Besides their function as a stabilizer and preservative, they may also act as antiseptic agents and furthermore may help in absorption. The methyl phenol may be o-cresol, m-cresol or p-cresol, but m-cresol is preferred.

25 As will be understood, the concentration of the pharmaceutical agent is an amount sufficient to be effective in treating or preventing a disorder or to regulate a physiological condition in an animal or human. The concentration or amount of pharmaceutical
30 agent administered will depend on the parameters determined for the agent and the method of administration, e.g. nasal, buccal, pulmonary. For example, nasal formulations tend to require much lower

- 15 -

concentrations of some ingredients in order to avoid irritation or burning of the nasal passages. It is sometimes desirable to dilute an oral formulation up to 10-100 times in order to provide a suitable nasal formulation.

Preferred methods of forming non-phospholipid membrane mimetic amphiphiles and phospholipid are based on the phase behaviour of lipid amphiphiles and phospholipids. Such methods use high turbulence or high shear methods of mixing, e.g. turbines or high velocity nozzles. For example, the membrane-mimetic amphiphiles may be injected at high velocity, e.g. through nozzles, into an aqueous phase of the phospholipid. Alternatively, the membrane mimetic amphiphiles and the phospholipids may be mixed in a mixing chamber into which the phospholipids are injected at high velocity through one or more nozzles and the membrane-mimetic amphiphiles are also injected at high velocity through one or more nozzles. Other ingredients, such as sodium lauryl sulphate, phenol and/or m-cresol, protease inhibitors may be premixed with either the membrane-mimetic amphiphile or the phospholipid. The velocity and mixing of the two liquids depends in part on the viscosities of the materials and nozzle diameters, e.g. 10 to 15 m/s through 0.5 to 1.0 mm diameter nozzle apertures. Typically the ratio of the membrane-mimetic amphiphile aqueous solution to the phospholipid solution is about 5:1 to about 20:1 and the temperature of mixing is typically from about 10°C to 20°C.

It may sometimes be necessary to heat the membrane-mimetic amphiphiles and other ingredients in order to yield a homogeneous aqueous solution prior to mixing with the phospholipids. The nature of the proteinic pharmaceutical may also dictate the temperature range at which mixing may take place. The temperature of mixing

- 16 -

is typically room temperature or below, but may be higher than room temperature for certain formulations. The resulting formulation contains multi-lamellar liposomal vesicles. If the formulation has been heated
5 during mixing, it is sometimes desirable to cool the mixture while still being mixed, in order to assist in the formation of the multi-lamellar vesicles.

Mixed multi-lamellar vesicles formed by the present process are very small in size, e.g. less than 10 nm,
10 and are stable under most storage conditions.

Preferably, the membrane-mimetic amphiphile solution is injected into the phospholipid solution through tangentially placed nozzles in a small cylindrical mixing chamber. Preferably, one or two
15 nozzles are used for the membrane-mimetic amphiphile solution and one or two alternating nozzles for the phospholipid solution. The two liquids are preferably delivered to the nozzles by flow-controlled positive displacement pumps.

20 The phenol and/or m-cresol are added to stabilize the formulation and protect against bacterial growth. An isotonic agent such as glycerin may also be added. The phenol and/or m-cresol and glycerin may be added after the membrane-mimetic amphiphile and phospholipids
25 have been mixed, if desired, rather than with the other ingredients.

After formation of the pharmaceutical formulation, the formulation is charged to a pressurizable container. Preferably the container is a vial suitable for use with
30 a metered dose dispenser, e.g. a metered dose inhaler or applicator. Then the vial is charged with propellant. As the propellant is introduced into the vial, there is great turbulence in the vial and the propellant and pharmaceutical formulation become mixed. Some of the
35 formulations with glycerin or polyglycerin in them tend

- 17 -

not to separate on standing. Others may separate. For those aerosol formulations which are substantially homogeneous, it may not be necessary to shake the vial before use, although, through habit with other formulations, many users may shake the vial. Shaking the vial is recommended, however, in order to assure good accuracy of pharmaceutical dispensing from "shot" to "shot" and from the first shot to the last from the container. As is known, in order to deliver the pharmaceutical agent to the lung, it is necessary for the user to breathe deeply when the aerosol spray from the pressurized container is released. Without breathing in, the pharmaceutical agent is delivered to the buccal cavity. The method chosen will depend on a number of factors, including the type of pharmaceutical agent, the concentration in the aerosol, the desired rate of absorption required and the like.

The preferred propellants are hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons, dimethyl ether and diethyl ether. Even more preferred is HFC 134a (1,1,1,2 tetrafluoroethane).

Although the present invention has such wide applicability, the invention is described hereinafter with particular reference to insulin and its analogues, which are used for the treatment of diabetes.

In the case of insulin, which is intended for administration through nasal or oral cavities or the lungs, an aqueous buffer solution may be made first by adding aqueous alkali metal C8 to C22 alkyl sulphate, e.g. sodium lauryl sulphate, to powdered insulin, and then stirring until the powder is dissolved and a clear solution is obtained. Typical concentrations of sodium lauryl sulphate in the aqueous solution are about 3 to 20 wt./wt.% in the solution. Typically, insulin is present in the solution in an amount which will give a

- 18 -

concentration of about 2 to 4 wt./wt.% of the final formulation.

The buffer solution is then added to liquid which comprises a membrane-mimetic amphiphile or a
5 phospholipid while mixing vigorously, to form multi-lamellar liposomal vesicles.

The membrane-mimetic amphiphile is selected from the group consisting of lauramidopropyl betain, lauramide monoisopropanolamide, sodium
10 cocoamphopropionate, bishydroxypropyl dihydroxypropyl stearammonium chloride, polyoxyethylene dihydroxypropyl stearammonium chloride, dioctadecyldimethylammonium chloride, sulphosuccinates, stearamide DEA, sodium tauro dihydro fusidate, fusidic acid, alkali metal isostearyl
15 lactylates, alkaline earth metal isostearyl lactylates, panthenyl triacetate, cocamidopropyl phosphatidyl PG-diammonium chloride, stearamidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl
20 phosphatidylcholine, polysiloxy pyrrolidone linoleyl phospholipid, octylphenoxypolythoxyethanol, and combinations thereof.

The phospholipid is selected from the group consisting of phospholipid GLA, phosphatidyl serine,
25 phosphatidylethanolamine, inositolphosphatides, dioleoylphosphatidylethanolamine, sphingomyelin, ceramides, cephalin, triolein, unsaturated lecithin, saturated lecithin and lysolecithin.

Each of the membrane-mimetic amphiphiles and
30 phospholipids are present in a concentration of from 1 to 10 wt./wt.% of the total formulation.

The phenol and/or m-cresol may be added with the membrane mimetic amphiphile, the phospholipid or at any other time during mixing.

35 Other ingredients may be added to the liposomal

- 19 -

solution. For example, flavouring agents, antioxidants, salts, protease inhibitors or other pharmaceutically acceptable compounds may be added.

In general the size of the multi-lamellar liposomal vesicle particles is about from 1 to 10 nm, and preferably from 1 to 5 nm. Such a size distribution ensures effective absorption of the formulation, and therefore the pharmaceutical agent, through the membranes, for example the membranes in the oral and nasal cavities.

The specific concentrations of the essential ingredients can be determined by relatively straightforward experimentation. For absorption through the nasal and oral cavities, it is often desirable to increase, e.g. double or triple, the dosage which is normally required through injection of administration through the gastrointestinal tract.

As will be understood, the amount of each component of the formulation will vary depending on the pharmaceutical agent and the site of application.

For oral application, sodium lauryl sulphate is insufficient on its own and must be combined with at least one membrane-mimetic amphiphile and at least one phospholipid to promote the oral absorption of macromolecules to achieve therapeutic effects. The effect is enhanced by delivery of the macromolecules by aerosol, with the additions of phenol and/or m-cresol to the formulation and using a propellant, particularly a hydrogen-containing fluorocarbon or a hydrogen-containing chlorofluorocarbon.

The oral aerosol formulations may be delivered with a suitable applicator.

Preferred formulations oral or nasal application have the following combinations, in addition to sodium lauryl sulphate:

- 20 -

i) ceramide and stearamidopropyl phosphatidyl PG-diammonium chloride;

ii) borage amidopropyl phosphatidyl PG-diammonium chloride and lecithin;

5 The therapeutic compositions of the present invention can be stored at room temperature or at cold temperature. Storage of proteinic drugs is preferable at a cold temperature, e.g. 4°C, to prevent degradation of the drugs and to extend their shelf life.

10 As indicated hereinbefore, generally, oral, pulmonary, transdermal and nasal are the favoured sites of the administration but the composition can be applied to the rectal and vaginal mucosa. According to the physiologically active peptide or protein used, the
15 dosage form and the site of administration a specific administration method can be selected.

 The composition of this invention is generally prepared as microfine multi-lamellar liposomal vesicle particles (1 to 10 nm or less) by the virtue of its
20 preparation methods used and combinations suitable characteristics of the membrane mimetic amphiphiles and phospholipids.

 Utilization of atomizer or aerosol spray devices (metered dose inhalers or nebulizers) can be used to
25 further reduce the particle size for effective inhalation from the nasal or oral cavity so the drug may successfully reach to the specific site, especially the lungs, and be absorbed.

 A particular advantage with the use of metered dose
30 dispensers is that the formulation can be delivered in a relatively precise dose, e.g. titratable to injection within 1 unit of insulin dose. The droplet size of the formulation preferably falls between 1-5 μm in order for droplets to penetrate buccal mucosa or to reach to the
35 deep lung surface. Thus, the present invention is

- 21 -

suitable for delivery of proteinic drugs such as insulin for the treatment of diabetes.

The pressurized dispensers also offer a wide dosing range and consistent dosing efficiency. With such a
5 delivery, greater than about 95% of the dose may reach the target area. The smaller particle size (1-5 μm) obtained using pressurized inhalers also enhances dosing due to broader coverage within the lung cavity. In this
10 situation, increased coverage can help more absorption of a drug like insulin. Furthermore, because these devices are self-contained, potential contamination is avoided.

- 22 -

CLAIMS:

1. An aerosol pharmaceutical formulation with multilamellar vesicles, comprising i) a pharmaceutical agent, ii) water, iii) an alkali metal C8 to C22 alkyl sulphate in a concentration of from 1 to 10 wt./wt.% of the total formulation, iv) at least one membrane-mimetic amphiphile, v) at least one phospholipid, vi) a phenol selected from the group consisting of phenol and methyl phenol in a concentration of from 1 to 10 wt./wt.% of the total formulation, and vi) a propellant selected from the group consisting of C1 to C2 dialkyl ether, butanes, fluorocarbon propellant, hydrogen-containing fluorocarbon propellant, chlorofluorocarbon propellant, hydrogen-containing chlorofluorocarbon propellant, and mixtures thereof,

wherein the membrane-mimetic amphiphile is selected from the group consisting of lauramidopropyl betain, lauramide monoisopropanolamide, sodium cocoamphopropionate, bishydroxypropyl dihydroxypropyl stearammonium chloride, polyoxyethylene dihydroxypropyl stearammonium chloride, dioctadecyldimethylammonium chloride, sulphasuccinates, stearamide DEA, sodium tauro dihydro fusidate, fusidic acid, alkali metal isostearyl lactylates, alkaline earth metal isostearyl lactylates, panthenyl triacetate, cocamidopropyl phosphatidyl PG-diammonium chloride, stearamidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidylcholine, polysiloxo pyrrolidone linoleyl phospholipid, octylphenoxypolythoxyethanol, and combinations thereof, and

wherein the phospholipid is selected from the group consisting of, phospholipid GLA (glycolic, lactic acid), phosphatidyl serine, phosphatidylethanolamine, inositolphosphatides, dioleoylphosphatidylethanolamine,

- 23 -

polysiloxy pyrrolidone linoleyl phospholipid, sphingomyelin, ceramides, cephalin, triolein, unsaturated lecithin, saturated lecithin and lysolecithin, and combinations thereof, and

5 wherein the amount of each membrane-mimetic amphiphile and phospholipid is present in a concentration of from 1 to 10 wt./wt.% of the total formulation, and the total concentration of membrane-mimetic amphiphiles and phospholipids is less than 50
10 wt./wt.% of the formulation.

2. A formulation according to Claim 1 wherein the alkali C8 to C22 metal alkyl sulphate is sodium lauryl sulphate.

3. A formulation according to Claim 1 wherein there
15 are at least two membrane mimetic amphiphiles.

4. A formulation according to Claim 1 wherein the membrane-mimetic amphiphile is selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid and mixtures
20 thereof, the concentration such absorption enhancing compound being from about 1 to about 5 wt./wt.%.

5. A formulation according to Claim 1 which contains sodium lauryl sulphate and combinations selected from the group consisting of:

25 i) ceramide and stearamidopropyl phosphatidyl PG-diammonium chloride; and

 ii) borage amidopropyl phosphatidyl PG-diammonium chloride and lecithin;

6. A formulation according to Claim 1 wherein the
30 pharmaceutical agent is selected from the group consisting of insulin, heparin, low molecular weight heparin, low molecular weight heparin, hirugen, hirulos, hirudin, interferons, interleukins, cytokines, mono and polyclonal antibodies, chemotherapeutic agents,
35 vaccines, glycoproteins, hormones bacterial toxoids,

- 24 -

growth hormones, calcitonins, insulin like growth factors (IGF), glucagon like peptides (GLP-1 or GLP-2), steroids and retinoids, injectable large molecule antibiotics, protein based thrombolytic compounds, platelet inhibitors, DNA, Gene therapeutics, RNA, antisense oligonucleotides, opioids, narcotics, analgesics, NSAIDS, steroids, anaesthetics, hypnotics and pain killers.

7. A formulation according to Claim 6 wherein the pharmaceutical agent is insulin.

8. A process for making a pharmaceutical composition comprising:

mixing in a high shear mixer a proteinic pharmaceutical agent, water, an alkali metal lauryl sulphate in a concentration of from 1 to 10 wt./wt.% of the total formulation, at least one membrane-mimetic amphiphile and at least one phospholipid,

wherein the membrane-mimetic amphiphile is selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, lauramidopropyl betain, lauramide monoisopropanolamide, sodium cocoamphopropionate, bishydroxypropyl dihydroxypropyl stearammonium chloride, polyoxyethylene dihydroxypropyl stearammonium chloride, dioctadecyldimethylammonium chloride, sulphosuccinates, stearamide DEA, gamma-linoleic acid, borage oil, evening of primrose oil, monoolein, sodium tauro dihydro fusidate, fusidic acid, alkali metal isostearyl lactylates, alkaline earth metal isostearyl lactylates, panthenyl triacetate, cocamidopropyl phosphatidyl PG-diammonium chloride, stearamidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidylcholine, polysiloxy pyrrolidone linoleyl phospholipid, trihydroxy-oxo-cholanylglycine and alkali

- 25 -

metal salts thereof, and octylphenoxypolythoxyethanol, polydecanol X-lauryl ether and polydecanol X-oleyl ether, wherein X is from 9 to 20, and

wherein the phospholipid is selected from the group
5 consisting of phospholipid GLA, phosphatidyl serine, phosphatidylethanolamine, inositolphosphatides, dioleoylphosphatidylethanolamine, sphingomyelin, ceramides, cephalin, triolein, lecithin, saturated lecithin and lysolecithin, and

10 wherein the amount of each membrane mimetic amphiphile and phospholipid is present in a concentration of from 1 to 10 wt./wt.% of the total formulation, and the total concentration of membrane mimetic amphiphiles and phospholipids is less than 50
15 wt./wt.% of the formulation;

said mixing being continued until the composition is in multilamellar vesicle form; and

adding a phenol selected from the group consisting of phenol, methyl phenol and mixtures thereof;

20 dispensing the resulting formulation into an aerosol container and charging the container with a propellant.

9. A process according to Claim 8 wherein the membrane-mimetic amphiphile is selected from the group
25 consisting of hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid and mixtures thereof, the concentration such absorption enhancing compound being from about 1 to about 5 wt./wt.%.

10. A process according to Claim 8 wherein the alkali
30 metal lauryl sulphate is sodium lauryl sulphate.

11. A process according to Claim 8 wherein the propellant is selected from the group consisting of hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons, dimethyl ether and diethyl
35 ether.

- 26 -

12. A process according to Claim 8 wherein the proteinic pharmaceutical agent is selected from the group consisting of insulin, heparin, so-called low molecular weight heparin, low molecular weight heparin, 5 hirugen, hirulos, hirudin, interferons, interleukins, cytokines, mono and polyclonal antibodies, chemotherapeutic agents, vaccines, glycoproteins, bacterial toxoids, hormones, calcitonins, insulin like growth factors (IGF), glucagon like peptides (GLP-1 or 10 GLP-2), large molecule antibiotics, protein based thrombolytic compounds, platelet inhibitors, DNA, RNA, gene therapeutics, antisense oligonucleotides, opioids, narcotics, analgesics, NSAIDS, steroids, anaesthetics, hypnotics and pain killers.

15 13. A process according to Claim 8 wherein the proteinic pharmaceutical agent is insulin.

14. A process according to Claim 8 wherein the method of mixing is a high turbulence or high shear method of mixing.

20 15. A process according to Claim 14 selected from the group consisting of i) injecting the phospholipid, in liquid form, at high velocity through at least one nozzle into an aqueous phase of the membrane-mimetic amphiphile, ii) injecting the membrane-mimetic 25 amphiphile, in liquid form, at high velocity through at least one nozzle into an aqueous phase of the phospholipid, and iii) injecting the phospholipid, in liquid form, at high velocity through at least one nozzle and the membrane mimetic amphiphile, in liquid 30 form, at high velocity through at least one nozzle into a mixing chamber; and

wherein the alkali metal lauryl sulphate is present with either the phospholipid or membrane-mimetic amphiphile.

35 16. A process according to Claim 15 wherein the

- 27 -

velocity the phospholipid and amphiphile liquids is from 0 to 15 m/s through 0.5 to 1.0 mm diameter nozzle apertures.

17. A process according to Claim 14 wherein the ratio
5 of the membrane-mimetic amphiphile aqueous solution to the phospholipid solution is about 5:1 to about 20:1.

18. A process according to Claim 15 wherein the ratio of the membrane-mimetic amphiphile aqueous solution to the phospholipid solution is about 5:1 to about 20:1.

10 19. A metered dose aerosol dispenser containing an aerosol pharmaceutical formulation with multilamellar vesicles, comprising i) a pharmaceutical agent, ii) water, iii) an alkali metal C8 to C22 alkyl sulphate in a concentration of from 1 to 10 wt./wt.% of the total
15 formulation, iv) at least one membrane-mimetic amphiphile, v) at least one phospholipid, vi) a phenol selected from the group consisting of phenol and methyl phenol in a concentration of from 1 to 10 wt./wt.% of the total formulation, and vi) a propellant selected
20 from the group consisting of C1 to C2 dialkyl ether, butanes, fluorocarbon propellant, hydrogen-containing fluorocarbon propellant, chlorofluorocarbon propellant, hydrogen-containing chlorofluorocarbon propellant, and mixtures thereof,

25 wherein the membrane-mimetic amphiphile is selected from the group consisting of lauramidopropyl betain, lauramide monoisopropanolamide, sodium cocoamphopropionate, bishydroxypropyl dihydroxypropyl stearammonium chloride, polyoxyethylene dihydroxypropyl
30 stearammonium chloride, dioctadecyldimethylammonium chloride, sulposuccinates, stearamide DEA, sodium tauro dihydro fusidate, fusidic acid, alkali metal isostearyl lactylates, alkaline earth metal isostearyl lactylates, panthenyl triacetate, cocamidopropyl phosphatidyl PG-

- 28 -

diammonium chloride, stearamidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidylcholine, polysiloxo pyrrolidone linoleyl phospholipid, octylphenoxypolythoxyethanol, and combinations thereof, and

wherein the phospholipid is selected from the group consisting of, phospholipid GLA (glycolic, lactic acid), phosphatidyl serine, phosphatidylethanolamine, inositolphosphatides, dioleoylphosphatidylethanolamine, polysiloxo pyrrolidone linoleyl phospholipid, sphingomyelin, ceramides, cephalin, triolein, unsaturated lecithin, saturated lecithin and lysolecithin, and combinations thereof, and

wherein the amount of each membrane-mimetic amphiphile and phospholipid is present in a concentration of from 1 to 10 wt./wt.% of the total formulation, and the total concentration of membrane-mimetic amphiphiles and phospholipids is less than 50 wt./wt.% of the formulation.

20. A metered dose aerosol dispenser according to Claim 19 wherein the alkali C8 to C22 metal alkyl sulphate is sodium lauryl sulphate.

21. A metered dose aerosol dispenser according to Claim 19 wherein there are at least two membrane mimetic amphiphiles.

22. A metered dose aerosol dispenser according to Claim 19 wherein the membrane-mimetic amphiphile is selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid and mixtures thereof, the concentration such absorption enhancing compound being from about 1 to about 5 wt./wt.%.

23. A metered dose aerosol dispenser according to Claim

- 29 -

19 which contains sodium lauryl sulphate and combinations selected from the group consisting of:

i) ceramide and stearamidopropyl phosphatidyl PG-diammonium chloride; and

5 ii) borage amidopropyl phosphatidyl PG-diammonium chloride and lecithin;

24. A metered dose aerosol dispenser according to Claim 19 wherein the pharmaceutical agent is selected from the group consisting of insulin, heparin, low molecular
10 weight heparin, low molecular weight heparin, hirugen, hirulos, hirudin, interferons, interleukins, cytokines, mono and polyclonal antibodies, chemotherapeutic agents, vaccines, glycoproteins, hormones bacterial toxoids, growth hormones, calcitonins, insulin like growth
15 factors (IGF), glucagon like peptides (GLP-1 or GLP-2), steroids and retinoids, injectable large molecule antibiotics, protein based thrombolytic compounds, platelet inhibitors, DNA, Gene therapeutics, RNA, antisense oligonucleotides, opioids, narcotics,
20 analgesics, NSAIDS, steroids, anaesthetics, hypnotics and pain killers.

25. A metered dose aerosol dispenser according to Claim 19 wherein the pharmaceutical agent is insulin.

26. A method for administering an aerosol
25 pharmaceutical formulation with multilamellar vesicles, comprising i) a pharmaceutical agent, ii) water, iii) an alkali metal C8 to C22 alkyl sulphate in a concentration of from 1 to 10 wt./wt.% of the total formulation, iv)
at least one membrane-mimetic amphiphile, v) at least
30 one phospholipid, vi) a phenol selected from the group consisting of phenol and methyl phenol in a concentration of from 1 to 10 wt./wt.% of the total formulation, and vi) a propellant selected from the group consisting of C1 to C2 dialkyl ether, butanes,

- 30 -

fluorocarbon propellant, hydrogen-containing fluorocarbon propellant, chlorofluorocarbon propellant, hydrogen-containing chlorofluorocarbon propellant, and mixtures thereof,

5 wherein the membrane-mimetic amphiphile is selected from the group consisting of lauramidopropyl betain, lauramide monoisopropanolamide, sodium cocoamphopropionate, bishydroxypropyl dihydroxypropyl stearammonium chloride, polyoxyethylene dihydroxypropyl
10 stearammonium chloride, dioctadecyldimethylammonium chloride, sulphosuccinates, stearamide DEA, sodium tauro dihydro fusidate, fusidic acid, alkali metal isostearyl lactylates, alkaline earth metal isostearyl lactylates, panthenyl triacetate, cocamidopropyl phosphatidyl PG-
15 diammonium chloride, stearamidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidyl PG-diammonium chloride, borage amidopropyl phosphatidylcholine, polysiloxo pyrrolidone linoleyl phospholipid, octylphenoxypolythoxyethanol, and
20 combinations thereof, and

 wherein the phospholipid is selected from the group consisting of, phospholipid GLA (glycolic, lactic acid), phosphatidyl serine, phosphatidylethanolamine, inositolphosphatides, dioleoylphosphatidylethanolamine,
25 polysiloxo pyrrolidone linoleyl phospholipid, sphingomyelin, ceramides, cephalin, triolein, unsaturated lecithin, saturated lecithin and lysolecithin, and combinations thereof, and

 wherein the amount of each membrane-mimetic
30 amphiphile and phospholipid is present in a concentration of from 1 to 10 wt./wt.% of the total formulation, and the total concentration of membrane-mimetic amphiphiles and phospholipids is less than 50 wt./wt.% of the formulation, by spraying a
35 predetermined amount of the formulation into the mouth

- 31 -

with a metered dose spray device.

27. A method for administration of a pharmaceutical agent according to Claim 26 wherein the formulation is sprayed into a buccal cavity of a human being, without
5 inhalation.

28. A method for administration of a pharmaceutical agent according to Claim 26 wherein the pharmaceutical agent is selected from the group consisting of insulin, heparin, low molecular weight heparin, hirulog, hirugen,
10 huridine, interferons, interleukins, cytokins, mono and polyclonal antibodies, immunoglobins, chemotherapeutic agents, vaccines, glycoproteins, bacterial toxoids, hormones, calcitonins, insulin like growth factors (IGF), glucagon like peptides (GLP-1), large molecule
15 antibiotics, protein based thrombolytic compounds, platelet inhibitors, DNA, RNA, gene therapeutics and antisense oligonucleotides and many injectable opioids, narcotics, hypnotics, steroids, pain killers and non-steroidal anti-inflammatory drugs.

20 29. A method for administration of a pharmaceutical agent according to Claim 26 wherein the pharmaceutical agent is insulin.

INTERNATIONAL SEARCH REPORT

National Application No

PCT/CA 99/01233

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/12 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 40057 A (ALLIANCE PHARMA ; TARARA THOMAS E (US); WEERS JEFFRY G (US); TREVIN) 19 December 1996 (1996-12-19) page 2, line 8 -page 2, line 12 page 2, line 19 -page 2, line 24 page 3, line 10 -page 3, line 26 page 7, line 16 -page 7, line 25	1-29
A	WO 97 42938 A (BIOZONE LAB INC) 20 November 1997 (1997-11-20) page 4, line 22 -page 5, line 2 page 5, line 15 -page 5, line 19 page 11, line 4 -page 11, line 17 -/-	1-29

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the International search

13 April 2000

Date of mailing of the International search report

08.05.00

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Borst, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 99/01233

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 004 611 A (LEIGH STEVEN) 2 April 1991 (1991-04-02) column 2, line 49 -column 2, line 61 column 3, line 16 -column 3, line 26 column 4, line 39 -column 4, line 64	1-29
Y	WO 96 36352 A (CHANDARANA SUBASH ;MODI PANKAJ (CA)) 21 November 1996 (1996-11-21) page 3, line 2 -page 3, line 21	1-29
A	SCHREIER H ET AL: "PULMONARY DELIVERY OF LIPOSOMES" JOURNAL OF CONTROLLED RELEASE,NL,ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, vol. 24, no. 1 / 03, 1 May 1993 (1993-05-01), pages 209-223, XP000303928 ISSN: 0168-3659 page 212, right-hand column, last paragraph -page 214, right-hand column, last paragraph	1-29
P,Y	WO 99 40932 A (MODI PANKAJ) 19 August 1999 (1999-08-19) page 5, line 6 -page 5, line 26 page 7, line 14 -page 7, line 30 page 8, line 5 -page 10, line 29	1-29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 99/01233

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 26-29 are directed to a method of treatment of the human/animal body, the search has been carried out (Rule 39.1(iv) PCT).
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 99/01233

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9640057 A	19-12-1996	AU 704918 B	06-05-1999
		AU 6153796 A	30-12-1996
		CA 2222063 A	19-12-1996
		CN 1195981 A	14-10-1998
		EP 0833608 A	08-04-1998
		HU 9900879 A	30-08-1999
		JP 11508237 T	21-07-1999
		NO 975321 A	27-01-1998
		PL 323931 A	27-04-1998
WO 9742938 A	20-11-1997	US 5891465 A	06-04-1999
		EP 0928189 A	14-07-1999
US 5004611 A	02-04-1991	AT 75606 T	15-05-1992
		DE 3585967 A	11-06-1992
		EP 0158441 A	16-10-1985
		JP 7053661 B	07-06-1995
		JP 61044808 A	04-03-1986
		US 5053217 A	01-10-1991
		US 5141674 A	25-08-1992
WO 9636352 A	21-11-1996	US 5653987 A	05-08-1997
		AU 5642396 A	29-11-1996
		CA 2210996 A	21-11-1996
		EP 0813421 A	29-12-1997
WO 9940932 A	19-08-1999	US 6017545 A	25-01-2000
		AU 2505399 A	30-08-1999

THIS PAGE BLANK (USPTO)